Introduction

Overview

In the three decades since AIDS was first reported, the National Institutes of Health (NIH) has been the global leader in research to understand, prevent, diagnose, and treat HIV and its many related conditions. Recent scientific advances resulting from NIH-funded research represent a turning point for AIDS research. New avenues for discovery have been identified, providing possibilities for the development of new strategies to prevent, treat, and potentially cure HIV. The NIH is leading global research efforts to capitalize on those advances, move science forward, and begin to turn the tide against this pandemic.

NIH research has resulted in landmark advances that have led to:

- *Co-discovery of HIV*, the virus that causes AIDS;
- *Development of the first blood test for the disease,* which has allowed diagnosis of infection as well as ensured the safety of the blood supply;
- *The critical discovery of key targets to develop antiretroviral therapy (ART) and multidrug regimens* that have resulted in improved life expectancy for those with access to and who can tolerate these drugs; and the development of treatments for many HIV-associated coinfections, comorbidities, malignancies, and clinical manifestations, with benefits for patients also suffering from those other diseases;
- *Groundbreaking strategies for the prevention of mother-to-child transmission,* which have resulted in dramatic decreases in perinatal HIV in the United States and in low-income countries;
- Demonstration that the *use of medical male circumcision can reduce the risk of HIV acquisition;*
- The first step in *proving the concept that a vaccine to prevent HIV infection is feasible*; and discovery of two potent human antibodies that can stop more than 90 percent of known global HIV strains from infecting human cells in the laboratory;
- Demonstration of the *first proof of concept for the feasibility of a microbicide gel capable of preventing HIV transmission*;
- Demonstration that the *use of therapy by infected individuals can dramatically reduce transmission* to an uninfected partner;
- Demonstration of the *potential feasibility of pre-exposure prophylaxis (PrEP)*, that long-term use of ART regimens by some groups of high-risk uninfected individuals can reduce risk of HIV acquisition;
- Discovery *that genetic variants may play a role in protecting some individuals*, known as "elite controllers," who have been exposed to HIV over an extended period, from developing symptoms and enabling them to control the infection without therapy;
- Critical *basic science discoveries* that continue to provide the foundation for novel research; and
- *Progress in both basic and treatment research efforts aimed at eliminating viral reservoirs in the body*, which is, for the first time, leading scientists to design and conduct research aimed at a cure.

NIH intramural and extramural researchers have produced two new exciting advances. NIH researchers published the results of studies utilizing potent human neutralizing antibodies that successfully suppressed a form of HIV in primates. This important research could potentially result in a new form of treatment for HIV that could be used as an adjunct to ART and could lead to opportunities for novel research to treat and potentially cure HIV. NIH-sponsored researchers also have made tremendous strides in producing and analyzing proteins that may provide an important new pathway in AIDS vaccine design.

The NIH is leading global research efforts to capitalize on all of these advances, move science forward, and begin to turn the tide against this pandemic.

HIV/AIDS Pandemic

Despite this progress, the HIV/AIDS pandemic will remain the most serious global public health crisis of our time. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reports that in 2013:

- More than 35 million people were estimated to be living with HIV/AIDS.
- About 2.1 million people became HIV-infected (about half of them women), or about 6,000 infected per day.
- 1.5 million people died of AIDS-related illnesses.

In the United States, HIV/AIDS continues to be an unrelenting public health crisis, disproportionately affecting racial and ethnic populations, women of color, young adults, and men who have sex with men. The Centers for Disease Control and Prevention (CDC) estimates that:

- Approximately 1.1 million people are HIV-infected.
- Approximately 50,000 new infections occur each year.
- One in four people living with HIV infection in the United States is female.

NIH AIDS Research Program

To address this pandemic, the NIH conducts and supports a comprehensive program of basic, clinical, translational, and behavioral research on HIV infection and its associated coinfections, opportunistic infections, malignancies, and other complications. AIDS research is carried out by all of the NIH Institutes and Centers (ICs) in accordance with their mission, in both intramural and extramural programs.

Key NIH Institutes and Centers Conducting AIDS Research

NATIONAL CANCER INSTITUTE: The National Cancer Institute (NCI) supports and conducts a broad range of research on HIV/AIDS, with a focus on AIDS-associated and non-AIDS-defining malignancies. NCI scientists co-discovered HIV and proved that the virus caused AIDS; developed the first blood test for HIV, which permits diagnosis of the disease and ensures the safety of the blood supply; conducted clinical trials of the first AIDS drugs; and developed the technology for the first vaccine for human papillomavirus (HPV), which can protect against cervical cancer (an AIDS-defining cancer) and other cancers. While the development of anti-HIV therapy has lowered the incidence of AIDS-defining cancers substantially, the number of non-HIV-defining cancers has been increasing as people infected with HIV live longer and the HIV-infected population overall increases in age. Cancer is now one of the leading causes, if not the leading cause, of death for people infected with HIV. NCI supports a wide range of basic, translational, and clinical research on malignancies associated with HIV infection, including research initiatives to address the increasing number of AIDS-defining malignancies in the developing world.

NIH AIDS RESEARCH PROGRAM

- Largest public investment in AIDS research in the world
- Encompasses all NIH Institutes and Centers
- Transcends every area of clinical medicine and basic scientific investigation
- Comprehensive program of basic, clinical, behavioral, and translational research on HIV infection, its associated coinfections, opportunistic infections, malignancies, and other complications
- Research or training projects in more than 100 countries
- Unprecedented trans-NIH scientific coordination and management of research funds

NATIONAL EYE INSTITUTE: The National Eye Institute (NEI) supports research on HIV-associated ophthalmic disorders, such as retinitis caused by cytomegalovirus (CMV) infection, and potential therapies for these disorders. Blindness is one of the many complications of HIV infection and AIDS. NEI also supports studies on the possible development of ocular toxic effects related to the treatment of HIV infection, as well as research on ocular comorbidities associated with HIV, such as herpes simplex virus.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE: As the HIV population ages, there has been a rise in the prevalence of chronic HIV-related cardiovascular, lung, and blood diseases. The mission of the National Heart, Lung, and Blood Institute (NHLBI) AIDS program is to support and facilitate research and training to address the emerging medical challenges facing the evolving HIV population. NHLBI is particularly interested in

encouraging collaboration between HIV specialists and heart, lung, and blood specialists to further expand knowledge about HIV-associated coronary artery disease, heart failure, hypertension, sudden cardiac death, smoking cessation, chronic obstructive lung disease, and pulmonary hypertension.

NATIONAL INSTITUTE ON AGING: The National Institute on Aging (NIA) works to improve the care of older adults with HIV/AIDS. The increasing prevalence of HIV in older Americans is due in large part to the improved survival of individuals receiving therapy and to ongoing new infections in older adults. Older adults with HIV are at risk of developing a variety of comorbid conditions, including cardiovascular disease, dyslipidemia, insulin resistance, and diabetes. NIA research addresses aging-related factors that contribute to the pathogenesis, disease progression, treatment, quality of life, and access to care among older HIV-infected individuals.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM: The National Institute on Alcohol Abuse and Alcoholism (NIAAA) supports epidemiologic, behavioral, and biomedical research exploring the complex and intertwined issues of alcohol abuse and HIV/AIDS. NIAAA supports research to understand the ecology and clinical epidemiology of alcohol use, abuse, and dependence in HIV-infected populations; understand the role of alcohol in disease progression and premature mortality related to co-occurring disease processes such as organ and tissue inflammation and immune response; develop and test interventions to decrease risky sexual and substance use behaviors and disseminate interventions in a wide range of settings; and improve medication adherence in alcohol-using and -abusing HIV-infected persons.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES: The National Institute of Allergy and Infectious Diseases (NIAID) is the largest Federal institute for HIV/AIDS research. NIAID conducts and supports an extensive range of basic and clinical domestic and international research to better understand HIV and how it causes disease; find new tools to prevent HIV infection, including a preventive vaccine, a microbicide, and treatment as prevention strategies; develop new and more effective treatments for people infected with HIV and related coinfections and comorbidities; and conduct research that can one day lead to a cure for HIV infection.

A key component of the NIH intramural program is the Dale and Betty Bumpers Vaccine Research Center (VRC). The primary focus of research is the development of vaccines for AIDS, but the VRC also is working on vaccines for other diseases, including Ebola virus, Marburg virus, and influenza. The VRC conducts a comprehensive program of research on the NIH intramural campus and works with scientists in academic, clinical, and industrial laboratories through a program of national and international collaborations. The potential scientific advances, methodologies, and resources also will provide the basis for research on vaccines for other diseases.

NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES: The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports research on skin immunity and integrity and chronic diseases of muscle and bone related to HIV-associated comorbidities and inflammatory conditions. Advances in degenerative muscle and bone conditions are particularly relevant to an aging HIV-AIDS patient population. NIAMS-sponsored HIV-related research includes studies on barrier and immune function in skin, which may provide important insights into the ability of HIV to enter the body through mucosal tissues and establish infection; the molecular mechanisms of muscle degeneration in HIV-infected and aging populations, and how it may be reversed; and the effects of HIV infection, ART, and aging on bones.

EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT: The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports and conducts research related to the unique features of HIV infection and AIDS in women, pregnant women, infants, children, adolescents, young adults, and families. Areas of focus for NICHD research include investigation of the biologic mechanisms of sexual transmission of HIV in the female genital tract; HIV interaction with endogenous and exogenous hormones; demographic and population-based studies related to sexual behavior; the interrelationship between HIV, pregnancy, and contraception; and research on HIV orphans and vulnerable children.

NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH: The National Institute of Dental and Craniofacial Research (NIDCR) supports studies on the oral manifestations and oral malignancies of HIV/AIDS. HIV-related oral opportunistic infections, coinfections, and malignancies represent early diagnostic indicators of HIV infection, disease progression, immunosuppression, optimal or suboptimal therapies, drug resistance, and treatment compliance. The NIDCR AIDS and Immunosuppression Program supports global, basic, translational, and clinical research.

NATIONAL INSTITUTE ON DRUG ABUSE: The National Institute on Drug Abuse (NIDA) supports a broad range of research to reduce the spread of HIV among drug abusers and their partners and to minimize the associated health and social consequences of the disease both domestically and internationally. Drug and alcohol intoxication is linked with increased HIV risk behavior, and injection and noninjection drug use continues to contribute significantly to the spread of HIV.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES: The National Institute of General Medical Sciences (NIGMS) supports research to answer critical scientific questions in cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, biomedical technology, bioinformatics, and computational biology, along with selected aspects of the behavioral sciences. NIGMS supports the structural characterization of HIV enzymes and viral proteins, which has been instrumental in the development of antiretroviral (ARV) drug therapies, such as protease inhibitors. NIGMS continues to support the characterization of viral proteins and is expanding its program to include cellular and viral complexes.

NATIONAL INSTITUTE OF MENTAL HEALTH: The National Institute of Mental Health (NIMH) supports a broad range of AIDS-related research. NIMH sponsors studies on the basic neuroscience of HIV infection, including research to elucidate the mechanisms underlying HIV-induced neuropath genesis; understand HIV-related motor and cognitive impairments; develop novel treatments to prevent or mitigate the neurobehavioral complications of HIV infection; and minimize the neurotoxicities induced by long-term use of ART. Eradication of the virus from HIV-infected individuals to achieve a cure or a functional cure is a high research priority. NIMH behavioral science research targets prevention of HIV transmission and acquisition, adherence to interventions to reduce the burden of disease, and studies that address the behavioral consequences of HIV/AIDS.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE: The National Institute of Neurological Disorders and Stroke (NINDS) supports basic, translational, and clinical research on the effects of chronic HIV infection and comorbidities on the central nervous system. NINDS-supported research includes studies of HIV-associated peripheral neuropathy; progressive multifocal leukoencephalopathy; cryptococcal meningitis;

cytomegalovirus infection; herpes virus infections; neuropathy; neurosyphilis; HIV-related psychological and neuropsychiatric disorders; and the effects of ART on the nervous system. Studies to define and elucidate novel mechanisms of pathogenesis that are driving neurocognitive decline at the intersection of HIV-associated neurodegenerative processes, aging-associated central nervous system disease, chronic highly active antiretroviral therapy (HAART) treatment effects, and host susceptibility factors also are priorities.

NATIONAL INSTITUTE OF NURSING RESEARCH: The National Institute of Nursing Research (NINR) sponsors domestic and international HIV/AIDS research focused on health promotion, disease prevention, and symptom management, including approaches to reduce HIV risk, develop and implement culturally appropriate HIV prevention education for adolescents, and overcome barriers to prevention in the United States and developing countries. NINR is focused on research to promote health and quality of life and prevention strategies across the course of HIV/AIDS disease, particularly in areas of symptom mechanism(s), biobehavioral interventions, prevalence disparity, age-related decisionmaking, and palliative and end-of-life care.

NATIONAL LIBRARY OF MEDICINE: The National Library of Medicine (NLM) works to translate biomedical research into practice. NLM's electronic information services deliver trillions of bytes of data to millions of users, including scientists, health professionals, and the public in the United States and around the globe every day. NLM's information resources include AIDSinfo—a service of the U.S. Department of Health and Human Services, managed by NLM with support from OAR and NIAID—that offers access to the latest, federally approved HIV/AIDS medical practice guidelines, HIV treatment and prevention clinical trials, and other research information for health care providers, researchers, people affected by HIV/AIDS, and the general public. In addition, NLM supports MEDLINE®/PubMed®, PubMed Central®, MedlinePlus®, and Medline Plus en español. MedlinePlus includes a series of HIV/AIDS-specific pages in English and Spanish. ClinicalTrials.gov provides the public with comprehensive information about all types of clinical research studies.

CENTER FOR SCIENTIFIC REVIEW: The Center for Scientific Review (CSR) ensures that NIH grant applications receive fair, independent, expert, and timely reviews. CSR organizes peer review groups composed of experienced and respected researchers from across the country and abroad that evaluate the majority of NIH grant applications for their scientific merit. These reviews allow NIH to fund the most scientifically promising research. All AIDS-related grant applications are reviewed by a study section or special emphasis panel within the AIDS and Related Research (AARR) Integrated Review Group on an expedited cycle mandated by Congress. AARR reviews grant applications in the areas of basic, translational, clinical, and behavioral aspects of HIV/AIDS research.

FOGARTY INTERNATIONAL CENTER: The Fogarty International Center (FIC) is the NIH focal point for international cooperation in biomedical research, facilitating the global exchange of ideas and collaborative research. FIC builds partnerships between health research institutions in the United States and in low- and middle-income countries to support and facilitate basic, clinical, and applied research and research training for investigators interested in addressing the global HIV pandemic. With co-funding from other NIH Institutes, Centers, and Offices, FIC provides support to HIV-related research and to the development of multidisciplinary biomedical and behavioral and social science research capacity for the prevention, care, and treatment of HIV/AIDS and HIV-related conditions for adults and children in low- and middle-income countries. The Fogarty HIV Research Training Program strengthens the capacity of researchers and institutions in low- and middle-income countries to conduct HIV-related research in their countries and to compete independently for research funding.

OFFICE OF RESEARCH INFRASTRUCTURE PROGRAMS: The Office of Research Infrastructure Programs (ORIP), a component of the Division of Program Coordination, Planning, and Strategic Initiatives in the NIH Office of the Director, supports the NIH's research infrastructure and research-related resources programs and coordinates the NIH's science education efforts. ORIP's infrastructure programs are designed to ensure that NIH effectively addresses and coordinates important areas of emerging scientific opportunities. The eight National Primate Research Centers and other ORIP-funded primate resources provide comprehensive support for investigators engaged in HIV/AIDS research using nonhuman primates, including studies of mechanisms of pathogenesis and development of vaccines and microbicides. ORIP also funds cooperative agreements that support a consortium of specific pathogen-free macaque breeding colonies that provide animals to investigators studying many aspects of HIV/AIDS.

NIH Office of AIDS Research

The Office of AIDS Research (OAR) *(http://www.oar.nih.gov/),* established in 1988, has unique legislative authorities unlike any other NIH entity to plan, coordinate, evaluate, and budget the entire NIH AIDS research program, which represents approximately 10 percent of the total NIH budget—the largest and most significant public investment in AIDS research in the world. OAR serves as the principal liaison with the U.S. Department of Health and Human Services, other Federal agencies, and domestic and international governmental and nongovernmental organizations on behalf of NIH AIDS-related research.

OAR serves as a model of trans-NIH planning and management, operating as an "Institute without walls," vested with primary responsibility for overseeing all NIH AIDS-related research, and thus allowing the NIH to pursue a united research front against the global AIDS epidemic.

AIDS research thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of every Institute and Center (IC). This diverse research portfolio demands an unprecedented level of trans-NIH scientific coordination and management of research funds. OAR coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research portfolio and sets the trans-NIH scientific priorities for this large and diverse program. Utilizing its legislative authorities, OAR has established comprehensive trans-NIH planning, budgeting, and portfolio analysis processes to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently.

OFFICE OF AIDS RESEARCH MISSION

Establish a unified NIH research agenda to address the AIDS pandemic through:

- Annual trans-NIH strategic planning process to identify highest scientific priorities and opportunities to address changing epidemic
- Annual trans-NIH budget based on Strategic Plan
- Trans-NIH coordination, management, and evaluation
- Facilitation and implementation of domestic and international collaborative AIDS research agreements

OAR identifies emerging scientific opportunities and public health challenges that require focused attention; manages and facilitates multi-Institute and trans-Institute activities to address those needs; fosters research by designating funds and supplements to jump-start or pilot program areas; sponsors reviews or evaluations of research program areas; and facilitates international AIDS research and training. OAR's unique budget authorities also allow it to transfer funds across ICs and across scientific areas.

OAR supports a number of initiatives to enhance dissemination of research findings to researchers, physicians, institutions, communities, constituency groups, and patients. OAR also has placed high priority on research and community outreach initiatives to address the disproportionate impact of the epidemic on racial and ethnic minority communities in the United States.

Trans-NIH Strategic Plan

Each year, OAR develops the Trans-NIH Plan for HIV-Related Research *(http://www.oar.nih.gov/strategicplan)*. The Plan is developed in collaboration with scientists from the NIH Institutes and Centers (ICs), other Government agencies, and nongovernmental organizations, as well as community representatives. During the planning process, the state of the science is reviewed, newly emerged and critical public health needs are assessed, and scientific opportunities are identified. The annual process culminates with the identification of the highest strategic priorities and critical research needs in each of the following scientific areas: Natural History and Epidemiology; Etiology and Pathogenesis; Microbicides; Vaccines; Behavioral and Social Science; Therapeutics; Treatment as Prevention; Training, Infrastructure, and Capacity Building; and Information Dissemination. Research Toward a Cure was added several years ago as a new scientific area of emphasis. The Plan also addresses research in special populations, including Women and Girls, Racial and Ethnic Populations, and Research in International Settings.

To facilitate tracking and analysis, OAR requires ICs to report all AIDS-related expenditures, including extramural, intramural, and research management and support, on a quarterly basis, to the OAR trans-NIH AIDS Research Information System (ARIS) database. Expenditures are coded by the ICs to the objective(s) of the Plan. This database also serves as the primary resource for AIDS research information in the Research Conditions and Diseases Categorization (RCDC) system.

THE STRATEGIC PLAN IS A UNIQUE AND CRITICAL DOCUMENT THAT SERVES AS THE FRAMEWORK FOR:

- Developing the annual AIDS research budget for each IC
- Determining the use of AIDS-designated dollars
- Developing the annual Presidential by-pass budget
- Tracking and monitoring all NIH AIDS research expenditures

OAR PLANNING PROCESS PARTICIPANTS

- Trans-NIH Coordinating Committees
- NIH ICs
- Other Government entities with research responsibilities (CDC, FDA, USAID, VA, DoD, HRSA, IHS)*
- Nongovernment experts from academia and foundations
- Community representatives
- Office of AIDS Research Advisory Council

* These Federal Government agencies are the Centers for Disease Control and Prevention, the Food and Drug Administration, the U.S. Agency for International Development, the Department of Veterans Affairs, and the Department of Defense, respectively.

OAR Budget Development Process

OAR is mandated to develop the annual trans-NIH AIDS research budget in partnership with the Institute and Centers (ICs) and explicitly tied to the objectives of the Strategic Plan. The law provides that OAR "shall receive directly from the President and Director of the OMB all funds available for AIDS activities of the NIH" for allocation to the ICs in accordance with the Plan.

Subsequently, however, an agreement with Congress established the tradition that rather than receiving a separate single appropriation, OAR would determine each IC's AIDS research allocation to be included within the IC total appropriation. It also was agreed that AIDS and non-AIDS research would grow at approximately the same rate, that is, as an "Institute without walls"; AIDS research, as determined by OAR, would grow at the same rate as the other Institutes. Thus, AIDS research has historically represented approximately 10 percent of the total NIH budget.

For all appropriated funds, the OAR Director and the NIH Director determine the total amount to be allocated for AIDS-related research within the overall NIH budget. Within that total, OAR develops each IC's allocation. The ICs submit their AIDS-related research budget requests to OAR, presenting proposed new, expanded, or recompeting program initiatives, coded to specific Plan objective(s). OAR reviews the IC initiatives in relation to the Plan, its priorities, and to other IC submissions to eliminate redundancy and/or to ensure cross-Institute collaboration. The unique budget authorities allow OAR to build each IC budget from the commitment base, rather than from the previous year's appropriation.

OAR BUDGET DEVELOPMENT PROCESS

1. ICs develop new or expanded program initiatives with budget requests for each scientific area.
2. OAR reviews IC initiatives in relation to the Plan and OAR priorities.
3. Consultations occur between the ICs and OAR throughout the process.
4. The budget is developed in consultation between the OAR Director and the NIH Director.
5. OAR allocates budget levels to each IC.

The careful determination of the balance of the research budget—among Institutes, across areas of science, between intramural and extramural research programs, between basic and clinical research, and between investigator-initiated and targeted research—requires a comprehensive knowledge of the science and of the ICs' portfolios. Dollars are allocated to the ICs based on the priorities of the Plan, scientific opportunities, and the ICs' capacity to absorb and expend resources for the most meritorious science—not on a formula. This process reduces redundancy, promotes harmonization, and ensures cross-Institute collaboration. At the time of the appropriation, OAR informs each IC of its AIDS-related budget allocation, specifying amounts for each approved initiative. OAR also has a 3 percent transfer authority to move dollars across ICs during the fiscal year.

Extraordinary Opportunities for FY 2015

This strategic Plan establishes the critical priorities for trans-NIH AIDS research. The advances made by NIH intramural scientists and extramural investigators have opened doors for new and exciting research opportunities to answer key scientific questions that remain in the search for strategies to prevent and treat HIV infection both in the United States and around the world. These advances also represent the building blocks for the development of the trans-NIH AIDS research budget.

The key scientific priorities for NIH AIDS research address the goals of the President's National HIV/AIDS Strategy as well as the HIV Care Continuum Initiative established by Presidential Executive Order. The priorities also are aligned with the NIH Director's themes.

In FY 2015, OAR will place highest priority on the following key areas:

- Basic research on HIV that will underpin further development of critically needed prevention methodologies, including vaccines.
- Innovative multidisciplinary research and international collaborations to develop novel approaches and strategies to eliminate viral reservoirs that could lead toward a cure or lifelong remission of HIV infection, including studies on viral persistence, latency, reactivation, and eradication.
- Research to develop better, less toxic treatments and to investigate how genetic determinants, sex, gender, race, age, nutritional status, treatment during pregnancy, and other factors—including adherence and stigma—interact to affect treatment success or failure and/or disease progression.
- Studies to address the increased incidence of comorbidities, including AIDS-associated malignancies; cardiovascular, neurological and metabolic complications; and premature aging associated with long-term HIV disease and antiretroviral therapy (ART).

Specific programmatic areas include:

ETIOLOGY AND PATHOGENESIS

The NIH supports a comprehensive portfolio of research focused on the transmission, acquisition, establishment, and maintenance of HIV infection and the causes of its associated profound immune deficiency and severe clinical complications. Research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, methodologies for diagnosis of HIV infection, and tools for monitoring disease progression and the safety and effectiveness of antiviral therapies. Groundbreaking strides have been made toward understanding the fundamental steps in the life cycle of HIV, the host–virus interactions, and the clinical manifestations associated with HIV infection and AIDS. Additional research is needed to further the understanding of the virus and how it causes disease, including studies to delineate how sex, gender, age, ethnicity, race, pregnancy, nutritional status, and other factors interact to influence vulnerability to infection and disease progression; determine the role of immune dysfunction and chronic inflammation in HIV pathogenesis; and further the understanding of

the development of HIV-associated comorbidities, such as cardiovascular, neurological, and other clinical complications, malignancies, and coinfections (including tuberculosis and hepatitis C).

Research examining the genetic determinants associated with HIV susceptibility, disease progression, and treatment response also is needed. These studies may lead to the development of customized therapeutic and preventive regimens formulated for an individual patient based on his or her genetic sequence. The NIH also prioritizes research examining the mechanisms by which HIV establishes and reactivates latent reservoirs of infection and studies that further the understanding of factors that are associated with the ability of the host to restrict HIV infection and/or mitigate HIV disease progression. A better understanding of these processes could help identify key targets for the development of new therapeutic and vaccine strategies to prevent or control HIV infection and possibly lead to a cure for HIV disease.

RESEARCH TOWARD A CURE

Research related to the potential for a cure or lifelong remission of HIV infection is a key NIH research priority, which currently involves research across a number of areas. The NIH plans to increase this area of research over the next 3 fiscal years focused on:

- **Pathogenesis studies:** Basic research on viral reservoirs, viral latency, and viral persistence, including studies on genetic factors associated with reactivation of the virus and other barriers to HIV eradication.
- **Animal models:** Identification and testing of various animal and cellular models to mimic the establishment and maintenance of viral reservoirs. These studies are critical for testing novel or unique strategies for HIV reactivation and eradication.
- **Drug development and preclinical testing:** Programs to develop and preclinically test new and better antiretroviral (ARV) compounds capable of entering viral reservoirs, including the central nervous system and brain.
- **Clinical trials:** Studies to evaluate lead compounds, drug regimens, and immune-based strategies capable of a sustained response to HIV, including clinical studies of drugs and novel approaches capable of eradicating HIV-infected cells and tissues.
- **Therapeutic vaccines:** Design and testing of vaccines that would be capable of suppressing viral replication and preventing disease progression.
- **Adherence/compliance:** Development and testing of strategies to maintain adherence/compliance to treatment, in order to improve treatment outcomes and reduce the risk of developing HIV drug resistance.

MICROBICIDES

A safe and effective microbicide will be an important asset to the HIV prevention toolkit. Microbicides are products, including ARV drugs and other agents, that could be applied topically or injected to prevent acquisition of HIV and other sexually transmitted infections (STIs). Microbicides could be used alone or in combination with other strategies. The NIH supports a comprehensive and innovative microbicide research program that includes the screening, discovery, development, preclinical testing, and clinical evaluation of microbicide candidates. The NIH supports basic science research aimed at

understanding how HIV crosses mucosal membranes and infects cells. In addition, the NIH supports behavioral and social science research on adherence to, and the acceptability and use of, microbicides among different populations. These projects include the safety of microbicide use during pregnancy and menopause; studies in adolescents and in men who have sex with men; and implementation research to better understand how to integrate a potential product into community prevention practices. Basic science and clinical studies have shown promise for the use of ARV-based microbicides as HIV prevention strategies. Followup studies are underway or being developed to test different ARV- and non-ARV-based products, microbicides combined with a contraceptive for multipurpose prevention, and microbicides combined with antimicrobial agents to prevent HIV and other STIs. Microbicide formulations and new technologies that enhance adherence, such as injectable products, nanofibers, films, suppositories, and intravaginal rings, also are being developed and studied.

VACCINES

The best long-term hope for controlling the AIDS pandemic is the development of safe, effective, and affordable AIDS vaccines that may be used in combination with other prevention strategies. The NIH supports a broad AIDS vaccine research portfolio encompassing basic, preclinical, and clinical research, including studies to identify and better understand potentially protective immune responses in HIV-infected individuals and studies of improved animal models for the preclinical evaluation of vaccine candidates. Information gained from these studies is being used to inform the design and development of novel vaccine strategies. Since the modest success of the RV144 trial in Thailand using a pox virus vector and HIV envelope protein boosts, the NIH has supported unprecedented international collaborative investigations to identify how specific immune responses may protect against HIV acquisition. Samples from the HVTN 505 trial in the United States with DNA and adenovirus vectors are being subjected to similar analyses to understand why that vaccine strategy failed to protect against HIV acquisition. To build on the knowledge gained from these studies, clinical trials in other populations and in other parts of the world with new and potentially improved products and alternative vectors have been designed and are currently underway. Recent data from several Phase I and Phase II vaccine clinical studies present new scientific opportunities for the development of improved HIV vaccine candidates.

BEHAVIORAL AND SOCIAL SCIENCE

As studies continue to define a role for the use of ARV medications for HIV prevention, the NIH is supporting research to understand how these drugs can best be used for prevention in specific populations and social contexts. The NIH will continue to study ways to change those behaviors and social contexts and to facilitate engagement and retention in HIV testing, prevention, and treatment services. The NIH is supporting research to address factors associated with the HIV Care Continuum, and specifically on HIV care outcomes. Investigations are focused not only on individual-level variables, but also on social and structural issues, such as the role of stigma, housing, employment, health care access, and interpersonal networks. Studies have suggested that modifying these variables can promote early access to medical care, reduce costs, extend life expectancy, and improve quality of life. The NIH will continue to develop new research methods that can be applied to behavioral and social science studies, as well as the integration of biomedical and behavioral strategies in clinical investigations. These include approaches to increase recruitment into clinical trials; enhance statistical analyses of behaviors, such as alcohol use, that can affect medication studies; and identify behavioral issues relevant to genetic or genomic studies.

DRUG DISCOVERY, DEVELOPMENT, AND TREATMENT

ART has resulted in improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities and side effects associated with ARV drugs. ART also has delayed the progression of HIV disease to the development of AIDS. Unfortunately, the treatment is beginning to fail in an increasing number of patients who have been on ART. These patients are experiencing serious drug toxicities and developing drug resistance. Recent epidemiologic studies have shown that the incidence of coinfections, comorbidities, AIDS-defining and non-AIDS-defining malignancies, and complications associated with long-term HIV disease and ART are increasing. These include tuberculosis, hepatitis C, metabolic disorders, cardiovascular disease, conditions associated with aging, and neurologic and neurocognitive disorders. The NIH supports a comprehensive therapeutics research program to design, develop, and test drugs and drug regimens. Under development are new combinations of drugs and sustained release formulations and delivery systems to maintain undetectable viral load, to overcome drug resistance and treatment failure, and to prevent and treat HIV-associated coinfections, comorbidities, and other complications. The program supports cure research with a focus on developing drugs and cell- and gene-based strategies that can target and eradicate persistent viral reservoirs in various cells, tissues, and organ systems, including the central nervous system and brain. This program also is supporting preclinical trials of innovative strategies to eliminate viral reservoirs, including testing therapeutic anti-HIV monoclonal antibodies with and without ARV drugs.

TREATMENT AS PREVENTION

A critical new area of prevention research is the study of treatment strategies as a method to prevent new HIV infections. This approach builds on NIH-sponsored landmark clinical trials that demonstrated that treatment of HIV-infected pregnant women could significantly reduce transmission of HIV from mother to child. Recent groundbreaking studies have demonstrated the successful use of ARVs to prevent transmission of HIV in specific populations. Clinical results from a large NIH-sponsored international clinical trial (HIV Prevention Trials Network [HPTN] 052) showed that early initiation of ART for HIV-infected heterosexual individuals resulted in a 96 percent reduction in sexual transmission of HIV to their uninfected partner. Another major NIH-sponsored clinical trial, the Chemoprophylaxis for HIV Prevention in Men study, also known as iPrEx, demonstrated that daily use of an ARV drug by some high-risk uninfected men could reduce their risk of acquiring HIV. The findings from this study showed proof of concept and the effectiveness of a novel HIV prevention strategy known as pre-exposure prophylaxis (PrEP). Recent studies have shown PrEP to be effective in preventing HIV acquisition among two at-risk populations: women in heterosexual discordant couples and injection drug users. The NIH supports ongoing basic, translational, clinical, and implementation research to develop combinations of ARV drugs and compounds that can be used in sustained release formulations for potential new PrEP strategies; test PrEP in high-risk uninfected populations, including adolescents; evaluate postexposure prophylaxis, the use of ART to prevent infection after HIV exposure, including in a health care setting; develop improved regimens to prevent mother-to-child transmission; and evaluate a potential innovative prevention strategy known as "test and treat" to determine the impact of increased testing with immediate referral to treatment at the community level.

NATURAL HISTORY AND EPIDEMIOLOGY

Natural history and epidemiologic research on HIV/AIDS is critical to the monitoring of epidemic trends, evaluation of prevention modalities, characterization of the clinical manifestations of HIV disease, and measurement of the effects of treatment regimens at the population level. Novel methodologies in the area of biostatistics, mathematical modeling, and laboratory technology have provided the basis for new epidemiological approaches in addressing HIV/AIDS. Multi-site epidemiologic studies in the United States are identifying new HIV-related comorbidities and helping to differentiate effects related to ART from those related to HIV disease. As the AIDS epidemic continues to evolve, there is a crucial need for epidemiologic studies in domestic and international settings. The NIH supports a comprehensive research portfolio in both settings to study the epidemiologic characteristics of populations in which HIV is transmitted and the changing spectrum of HIV-related disease (including the occurrence of coinfections, malignancies, metabolic, cardiovascular, neurological, skeletal, and other complications). These studies have delineated the significant health disparities that are critical factors in the epidemic (e.g., racial and ethnic disparities in the United States; between industrialized and resource-constrained nations; between men and women; and health disparities based on sexual identity). Ongoing observational studies are adding focus on at-risk individuals from the rural South in the United States as well as on individuals over the age of 50. Research on HIV-related health disparities and their impact on treatment access and effectiveness, as well as HIV prevention, will continue to be an NIH AIDS research priority.

TRAINING, INFRASTRUCTURE, AND CAPACITY BUILDING

The NIH supports the training of domestic and international biomedical and behavioral HIV researchers. The NIH also provides infrastructure and capacity building support as integral aspects of its commitment to carrying out scientifically and ethically sound and highly productive HIV-related research. The expansion of NIH-funded HIV research globally has necessitated the development of research training and infrastructure and capacity-building efforts in many resource-limited settings throughout the world. NIH-funded programs have increased the number of training positions for HIV-related researchers, including domestic and international programs specifically designed to recruit individuals from populations underrepresented in research into research careers and to build research capacity at minority-serving institutions in the United States. Equipment, shared instrumentation, and tissue and specimen repositories are examples of the research infrastructure and capacity-building support that the NIH provides to strengthen the conduct of AIDS-related research, both domestically and internationally.

INFORMATION DISSEMINATION

The NIH supports initiatives to enhance dissemination of research findings; develop and distribute state-of-the-art treatment and prevention guidelines; and enhance recruitment and retention of participants in clinical studies. Effective information dissemination approaches are an integral component of HIV prevention and treatment efforts. These efforts are crucial in light of the advent of new and complex ART regimens, issues related to adherence to prescribed treatments, and the need to translate behavioral and social prevention approaches into practice. The changing pandemic and the increasing number of new infections in specific population groups in the United States underscore the need to disseminate HIV research findings and other related information to communities at risk, such as racial

and ethnic populations, women, older individuals, and men who have sex with men. The flow of information among researchers, health care providers, and the affected communities represents additional opportunities to use new and emerging technologies to speed the translation of research results into practice and to shape future research directions.

Global Impact of NIH AIDS Research: Research to address the global pandemic is essential. AIDS research represents the largest component of the total NIH global research investment. Since the early days of the epidemic, the NIH has maintained a strong international AIDS research portfolio that has grown to include projects in approximately 100 countries around the world. NIH AIDS research studies are designed so that the results are relevant for both the host nation and the United States. These research programs also enhance research infrastructure and training of in-country scientists and health care providers. New collaborations have been designed to improve both medical and nursing education as a mechanism to build a cadre of global health leaders. Most of these grants and contracts are awarded to U.S.-based investigators to conduct research in collaboration with in-country scientists; some are awarded directly to investigators in international scientific, academic, or medical institutions.

Benefits of AIDS Research to Other Areas: It is essential to point out that AIDS research also pays extensive dividends in many other areas of biomedical research, including in the prevention, diagnosis, and treatment of many other diseases. AIDS research:

- Has deepened our understanding of immunology, virology, microbiology, molecular biology, and genetics.
- Is helping to unravel the mysteries surrounding so many other diseases because of the pace of discovery and the unique nature of HIV (i.e., the way the virus enters a cell; causes infection; affects every organ system; and unleashes a myriad of opportunistic infections, comorbidities, cancers, and other complications).
- Continues to make discoveries that can be applied to other infectious, malignant, neurologic, autoimmune, and metabolic diseases, as well as to the complex issues of aging and dementia.
- Has led to more effective drugs for multiple bacterial, mycobacterial, and fungal diseases and fostered significant improvements in drug design technologies.
- Has led to the development of new models to test treatments for other diseases in faster, more efficient, and more inclusive clinical trials.
- Continues to benefit patients undergoing cancer chemotherapy and patients receiving anti-transplant rejection therapy as a result of drugs developed to prevent and treat AIDS-associated opportunistic infections.
- Has advanced understanding of the relationship between viruses and cancer.

Most recently, the development of protease inhibitors to treat HIV has led to development of a new drug combination that can cure hepatitis C, which affects about 150 million people globally. That advance in hepatitis C research may, in turn, provide important knowledge toward an HIV cure. New investments in AIDS research will continue to fuel biomedical advances and breakthroughs that will have profound benefits far beyond the AIDS pandemic.

Conclusion

The recent scientific advances resulting from NIH-funded research represent a turning point for AIDS research. New avenues for discovery have been identified, providing possibilities for the development of new strategies to prevent, treat, and potentially cure HIV. Despite these advances, however, AIDS is not over, and it is far too soon to declare victory. Serious challenges lie ahead. There is little doubt that, despite our progress to date, the AIDS pandemic will continue to affect virtually every sector of society in nearly every nation in the world for decades to come. In light of this reality, the U.S. national commitment to AIDS research remains strong.

This strategic Plan represents the collective professional judgment of scientific experts from around the country and throughout the world on the highest priority areas of scientific opportunity to move us forward from this important moment in science. This Plan is designed to identify critical research to find new tools to begin to turn the tide in the fight against AIDS—so that we can all once again live in a world without AIDS.